Translational research for better diagnosis and treatment of endometrial cancer

Final Symposium

BioEndoCar

24th and 25th March 2022, Portorož, Slovenia

BOOK OF ABSTRACTS

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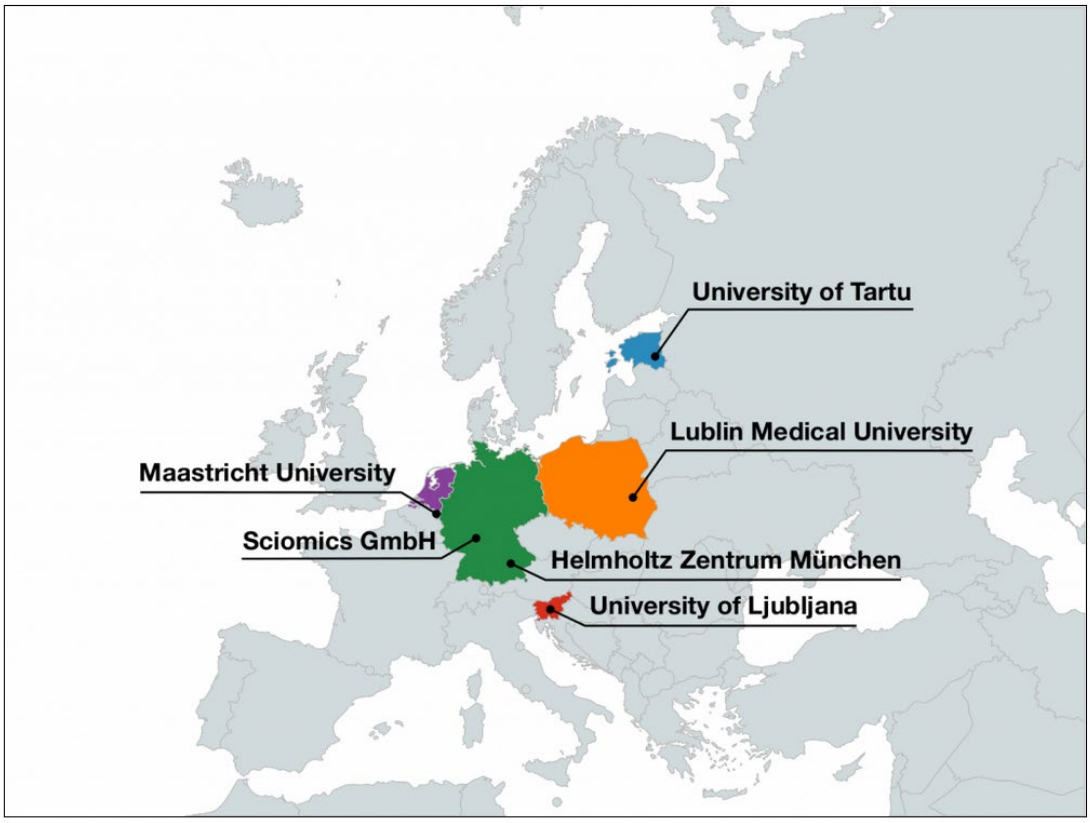

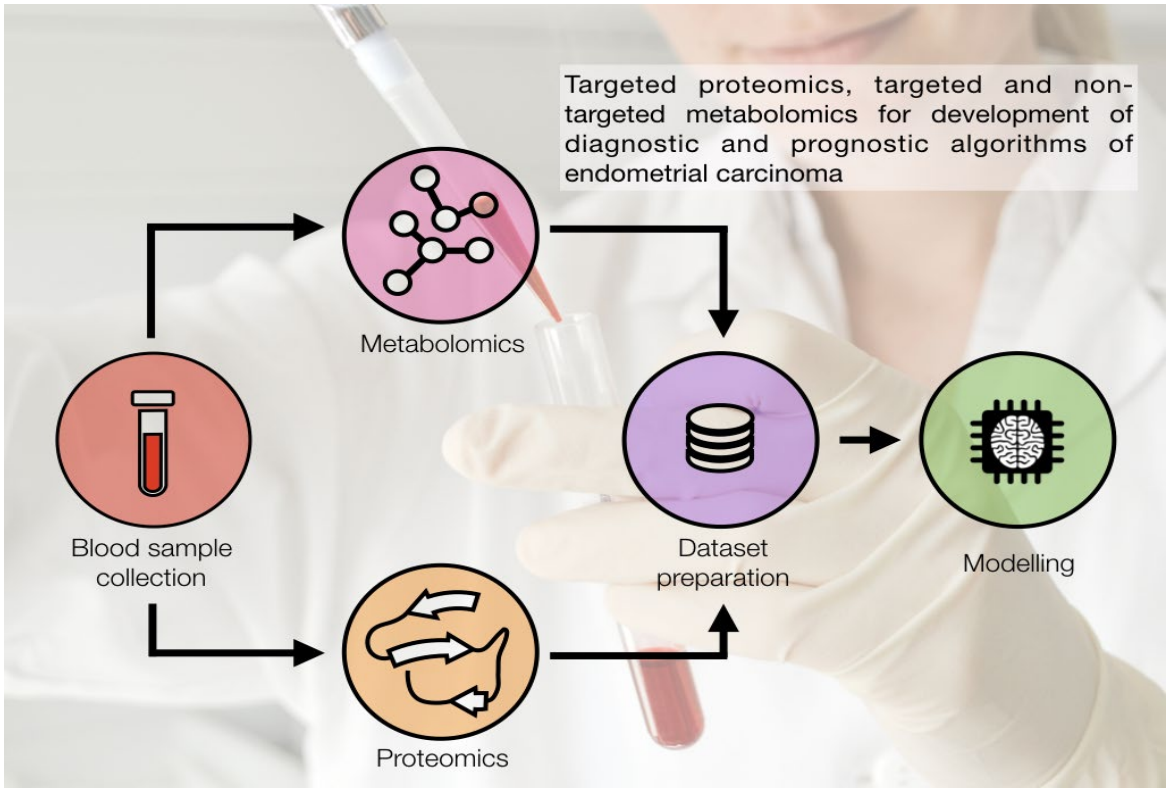

The **BioEndoCar** project addressed the lack of non-invasive diagnostic and prognostic biomarkers for endometrial cancer (EC).

EC is the most common gynaecological malignancy in the developed world, with 417,367 new cases and 97,370 deaths in 2020. The incidence and mortality of EC are still increasing. Although most EC patients are postmenopausal, 14% of patients are premenopausal, of which 4% are in the reproductive age. Furthermore, most patients are diagnosed and treated at an early stage, but cancer recurs in 15–20% of patients with no signs of advanced disease at the time of primary intervention.

Non-invasive diagnostics would reduce the requirement for biopsies and would serve as a screening test for early diagnosis of cancer, for prognosis and preoperative stratification of EC patients with a high risk of progression and recurrence, who need radical surgery and adjuvant chemo/radio therapy.

Biomarkers can facilitate the early diagnosis of asymptomatic patients and the identification of patients who are likely to progress and experience cancer recurrence. Furthermore, biomarkers can contribute to reducing overtreatment of EC patients with good prognosis. As an individual biomarker cannot provide sufficient sensitivity and specificity, identifying biomarker panels is crucial. Thus, the development of clinically applicable biomarker-based diagnostics requires global “omics” approaches. The combination of omics-derived biomarkers with clinical data can help identify algorithms with even better diagnostic characteristics.

BioEndoCar aimed to identify diagnostic metabolite and protein biomarkers for early detection of EC in asymptomatic high-risk population and prognostic biomarkers for identification of patients with poor prognosis by employing non-targeted and targeted metabolomic and semi-targeted proteomic approaches. The analytical approaches were combined with bioinformatics/biostatistical analysis to derive diagnostic and prognostic algorithms based on blood metabolites, proteins, and clinical data. The methodological approaches and results of this project will be presented at the Final Symposium.

Dear attendees,

The Final Symposium of the BioEndoCar project is organized as a two-day hybrid event and includes eight sessions that will focus on clinical aspects of endometrial cancer, from diagnosis, classification, prognosis, and management; on the importance of biobanking and national clinical data repositories; omics approaches for biomarker discovery and personalized treatment; and experimental models of endometrial cancer. In addition, one session will be dedicated to short oral presentations selected from the submitted abstracts. The Symposium will conclude with the keynote lecture providing future directions in endometrial cancer management by Dr. Johanna Pijnenborg, chair of the European Network for Individualised Treatment of Endometrial Cancer (ENITEC). We are looking forward to listening to the 28 lectures by clinicians and researchers from The Netherlands, Germany, Poland, Estonia, Czech Republic, Italy, Norway, Spain, and Slovenia. The internationally renowned speakers guarantee that the Symposium will provide the most up-to-date knowledge on diagnosis, prognosis, and new options for patients'-oriented treatment of endometrial cancer as well as an overview of state-of-the-art approaches for biomarker discovery.

We would like to thank all the speakers who contributed to the high quality of this Symposium and everyone involved in the organization of this hybrid event.

Chair and co-chair of the Final Symposium

Tea Lanišnik Rižner
Andrea Romano

BioEndoCar

Translational research for better diagnosis and treatment of endometrial cancer

Final Symposium of the BioEndoCar project

24th and 25th March 2022, Portorož, Slovenia

BOOK OF ABSTRACTS

Programme

Thursday 24th of March, 8:45 -16:20

8:45	**Welcome**
	Rector of the University of Ljubljana, Prof. Dr. Gregor Majdič
8:55	**Presentation of the BioEndoCar project**
	Tea Lanišnik Rižner, University of Ljubljana, Slovenia Andrea Romano, Maastricht University, The Netherlands
9:05-10:35	**Clinical challenges and management of patients with endometrial cancer**
	Chairperson: Johanna Pijnenborg and Jure Knez
9:05-9:30	**Current challenges in endometrial cancer** Henrica Werner, Maastricht University Medical Centre, The Netherlands
9:30-9:55	**Classification, histology, immunohistochemical markers, pathology evaluation and TCGA/promise** Michele Paudice, Dept. of Integrated Surgical and Diagnostic Sciences, Genoa, Italy
9:55-10:20	**UPDATE on the ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma** Umberto Leone, IRCCS National Cancer Institute, Milan, Italy
10:20-10:35	**Immune-therapy in the treatment of endometrial cancer** Mara Mantiero, IRCCS National Cancer Institute, Milan, Italy
10:35-10:50	**Coffee break**
10:50-11:55	**Current diagnostics and prognostics**
	Chairpersons: Andrzej Semczuk and Umberto Leone
10:50-11:15	**Current diagnostics in endometrial cancer** Jure Knez, University Medical Centre Maribor, Slovenia
11:15-11:40	**Current prognostics in endometrial cancer: Preoperative risk stratification models** Vít Weinberger, University Hospital Brno, Czech Republic
11:40-11:55	**External validation study of endometrial cancer preoperative risk stratification (ENDORISK) model** Petra Vinklerová, University Hospital Brno, Czech Republic
11:55-12:10	**Coffee break**

12:10-13:05 Management of specific patients' subgroups

Chairpersons: Vit Weinberger and Jure Knez

12:10-12:35 **Fertility sparing methods in adolescents affected by endometrial cancer**
Andrzej Semczuk, Medical University Lublin, Poland

12:35-12:50 **How to manage elderly patients with endometrial cancer**
Vita Andreja Mesarič, University Medical Centre Ljubljana, Slovenia

12:50-13:05 **How to manage patients at hereditary risk of endometrial cancer**
Fabio Barra, University of Genoa, Italy

13:05-13:45 Short oral presentations

Chairperson: Andrea Romano

Molecular characterization of endometrial cancer: a single-institution preliminary experience
Michele Paudice, Dept. of Integrated Surgical and Diagnostic Sciences, Genoa, Italy

Inter-component immunohistochemical assessment of selected proliferative markers in uterine carcinosarcomas
Andrzej Semczuk, Lublin Medical University, Poland

Serous endometrial carcinoma and pathogenic variants in genes of homologous recombination
Luka Kovač, University Medical Centre Ljubljana, Slovenia

Immunotherapy in endometrial carcinoma
Boštjan Pirš, University Medical Centre Ljubljana, Slovenia

PTmomics for biomarker discovery and personalized treatment
Nadine Stroh, Sciomics GmbH, Heidelberg, Germany

13:45-15:00 Lunch break

15:00-16:20 Importance of biobanking and national clinical data repositories

Chairpersons: Andrea Romano and Janina Tokarz

15:00-15:25 **What should clinicians and researchers know about biobanking**
Norman Klopp, Hannover Unified Biobank, Hannover, Germany

15:25-15:50 **IKNL and the Netherlands cancer registry**
Maaike van der Aa, IKNL, Utrecht, The Netherlands

15:50-16:05 **Slovenian population-based cancer registry – A database for monitoring national cancer burden and cancer care**
Vesna Zadnik, Institute of Oncology, Ljubljana, Slovenia

16:05-16:20 **Slovenian Biobank: Where we qre and where we are going?**
Urban Bren, University of Maribor, Slovenia

17:00-20:00 Boat tour and dinner

Friday 25th of March, 9:00 - 14:10

9:00-10:25 Omics for biomarker discovery and personalized treatment I

Chairpersons: Tea Lanišnik Rižner and Monika Sobočan

9.00-9:25 **Affinity-proteomics pipeline for a robust protein biomarker discovery and verification.**
Christoph Schröder, Sciomics GmbH, Heidelberg, Germany

9:25-9:40 **BioEndoCar: Identification of protein biomarker candidates for endometrial cancer using the ScioDiscover platform**
Camille Lowy, Sciomics GmbH, Heidelberg, Germany

9:40-9:55 **Experience the next generation multiplexing with Luminex® xMAP® INTELLIFLEX system**
Igor Pongrac, Life Science, Research & Applied Merck, Ljubljana, Slovenia

9:55-10:10 **Angiogenic factors as diagnostic and prognostic biomarker candidates for endometrial cancer**
Luka Roškar, University Medical Centre Ljubljana, Slovenia

10:10-10:25 **Approaching a non-invasive diagnosis of endometrial cancer by the analysis of protein biomarkers in cervical samples**
Eva Coll-de la Rubia, Vall d´Hebron Research Institute, Barcelona, Spain

10:25-10:40 Coffee break

10:40-11:50 Omics for biomarker discovery and personalized treatment II

Chairpersons: Tea Lanišnik Rižner and Christoph Schröder

10:40-11:05 **Study design for omics studies revisited**
Jerzy Adamski, Helmholtz Zentrum Munich, Germany

11:05-11:20 **Targeted and nontargeted metabolomics approaches in BioEndoCar**
Janina Tokarz, Helmholtz Zentrum Munich, Germany

11:20-11:35 **Machine learning for OMICS data analysis**
Dmytro Fishman, University of Tartu, Estonia

11:35-11:50 **Identification of protein biomarkers in FFPE primary tissues to predict recurrence in endometrial cancer**
Carlos Lopez Gil, Vall d´Hebron Research Institute, Barcelona, Spain

11:50-12:05 Coffee break

12:05-13:15 Experimental models of endometrial cancer

Chairpersons: Andrea Romano and Johanna Pijnenborg

12:05-12:20 ***In vitro* modeling in endometrial cancer**

Monika Sobočan, University Medical Centre Maribor, Slovenia

12:20-12:35 **Three-dimensional models to accelerate therapeutic discoveries *in vitro***
Vesna Kokondoska, Kemomed d.o.o. Ljubljana, Slovenia

12:35-12:50 **Estrogens and androgens in endometrial cancer**
Renata Pavlič/Marija Gjorgoska, University of Ljubljana, Slovenia

12:50-13:15 **Modelling endometrial cancer *in vivo***
Camilla Krakstad, University of Bergen, Norway

13:15 - 13:25 Coffee break

13:25-13:55 Keynote lecture

Chairpersons: Henrica Werner and Iztok Takač

Future directions in endometrial cancer management
Johanna Pijnenborg, Radboud University Medical Center, Nijmegen, The Netherlands

13:55-14:10 Conclusions

Tea Lanišnik Rižner, University of Ljubljana Slovenia
Andrea Romano, Maastricht University, The Netherlands

14:10 - 15:30 Lunch

Free time or walk to Piran

20:00 Farewell dinner

Section 1

Clinical challenges and management of patients with endometrial cancer

Current challenges in endometrial cancer

Henrica Werner
[1]*Maastricht University Medical Centre, Maastricht, the Netherlands*
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In this talk three topics are highlighted. Endometrial cancer (EC) is the most frequent malignancy in women in the more affluent countries. Through the rising life expectancy and rising prevalence of obesity worldwide, EC incidence will continue to increase. Considering all cancer types, EC incidence has the strongest positive correlation with body mass index. The underlying mechanisms linking obesity to EC are complex and include unopposed oestrogen stimulation alongside possibly obesity-mediated inflammation and insulin resistance. Obesity affects treatment options and is thus not only a causative factor. Until now, preoperative histology, grade, and if available, depth of invasion, supported the type of surgery advised. In spite of a low but realistic risk of lymph node metastases in low grade cancers, nodal dissection is not advised there. Also, preoperative biopsies are known to be inaccurate in up to 30% of cases. A number of recent developments aimed to refine this risk stratification, including sentinel node procedure, molecular classification and preoperative biomarkers will be discussed. Finally systemic treatment is given in the adjuvant and recurrent setting. The molecular stratification may importantly support the adjuvant treatment choice in EC, and this is investigated in a number of upcoming studies. In the recurrent setting; chemotherapy, immune therapy and hormonal treatment are valid alternatives and biomarkers may assist in treatment selection.

Classification, histology, immunohistochemical markers, pathology evaluation and TCGA/promise

Paudice Michele[1], Ferrero Simone[2]
[1]*Department of Integrated Surgical and Diagnostic Sciences (DISC), Genoa, Italy*
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Histopathological evaluation including subtyping and grading is the current cornerstone for classification of endometrial cancer. This provides clinicians with prognostic information and input for further therapy recommendations. Nonetheless, women with histologically similar endometrial cancers may have very different outcomes, particularly, those with high-grade cytology. In the recent years, four molecular subgroups of endometrial cancer have undergone extensive studies: POLE ultramutated (POLEmut), mismatch repair deficient (MMRd), p53 mutant (p53abn) and those endometrial cancer lacking any of these alterations, referred to as NSMP (non-specific molecular profile). Several large studies are confirming the prognostic relevance of these molecular alterations. However, this 'histo-molecular' approach has so far not been implemented in clinical routine. In the next years, the added value of integrating molecular parameters in adjuvant treatment decisions will be determined.

UPDATE on the ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Umberto Leone[1]
[1]*IRCCS National Cancer Institute, Milan, Italy*
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This talk will discuss the last European guidelines on the management of patients with endometrial cancer developed and published in 2021. In 2014, a European consensus conference on endometrial carcinoma produced multi-disciplinary evidence-based guidelines on selected questions. Given the large body of literature on the management of endometrial carcinoma published since 2014, the European Society of Gynaecological Oncology (ESGO), the European SocieTy for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) jointly decided to update these evidence-based guidelines and to cover new topics to improve the quality of care for women with endometrial carcinoma across Europe and worldwide. The main update in the new guidelines is the introduction of the molecular classification to identify prognostic groups analogous to the TCGA molecular-based classification. The new guidelines recommend the use in the clinical practice of the molecular analysis to be performed by the TCGA surrogate using a simplified diagnostic algorithm provided. These information are essential to plan the need and the type of adjuvant treatment after surgery.

Immune-therapy in the treatment of endometrial cancer

Mara Mantiero[1]
[1]*Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy*
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Endometrial cancer is the fourth most common malignancy in women and the most common gynecologic cancer in developed countries. Recently, the oncologic treatment of EC was implemented by genetic evaluation (mutations and polymorphisms) in order to identify important molecules for the control of tumor growth. In particular, about 15% of EC are microsatellite instability hypermutated (MSI-H), with high mutation rate related to alteration of MLH1, MSH2, MSH6, PMS2 genes involved in the mismatch repair (MMR) system. Especially, but not only, in this subgroup, the most important international regulatory authority (FDA, EMA etc.) approved the use of immunotherapy thanks to the positive results of different international clinical trials. Pembrolizumab, a PD1 blockade, is the first immune checkpoint inhibitor (ICB) whose clinical activity has been investigated in EC. In 2019 a phase II KEYNOTE-158 study evaluated pembrolizumab in MMR deficient (MMRd) noncolorectal carcinoma: this study enrolled 49 patients with progressive MSI EC. EC was one of the tumor types with the most frequent complete response (CR) in this study (41%). Moreover, also Dostarlimab an other PD-1 inhibitor, was approved on results from the dMMR endometrial cancer cohort of the GARNET study; this trial showed a 42.3% of objective response rate (ORR) in 71 patients with dMMR recurrent or advanced endometrial cancer. This included a 12.7% complete response (CR) rate and a 29.6% partial response (PR) rate. Another important aspect of this new drugs is the duration of response (DOR); in the GARNET trial DOR was at least 6 months for 93.3% of responders, and the median DOR was not reached at a median follow-up of 14.1 months (2.6-22.4+). Finally, recently was also approved the combination of immunotherapy (Pembrolizumab) with Lenvatinib (multiple-receptor tyrosine kinase inhibitor) for the treatment of patients with advanced endometrial cancer without microsatellite instability–high or mismatch repair deficient, who have disease progression following prior systemic treatment. In my presentation I will explain this new interesting therapeutic approaches for EC.

Section 2

Current diagnostics and prognostics

Current diagnostics in endometrial cancer

Jure Knez[1]
[1]*University Medical Centre Maribor*
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The approach to diagnostics of women with suspected endometrial cancer has evolved significantly in the last decade. In part, this is a consequence of better access to high quality imaging modalities and better diagnostic tools available today. On the other hand, the introduction of molecular classification of endometrial cancer is also changing our perception of the disease and is generating new possibilities of disease characterisation. Transvaginal ultrasound examination is today the fundamental non-invasive tool in the process of diagnostics and should be the first tool used in the assessment of endometrium. This allows for reliable exclusion of endometrial cancer or as a guide to further more invasive methods to obtain an endometrial biopsy. On the other hand, ultrasound is also of significant value in preoperative assessment of women with endometrial cancer in predicting local spread of the disease. It has been shown that ultrasound-based risk models can reliably predict the risk of lymph-node metastasis. In recent years, data is also emerging suggesting possible use of computer aided analysis of ultrasound images and deep learning technology to identifying high-risk disease in the group of women with endometrial cancer. In addition, molecular cancer characterisation has opened new minimally invasive possibilities in diagnostics. Using liquid-based cytology to upgrade conventional cytological analysis with genomic examination of endometrial cytology specimens, thus preserving high-quality DNA in the samples, could allow for rapid diagnosis and molecular classification of endometrial cancer. Liquid biopsy options, specifically, circulating cell-free DNA (cfDNA) analysis could provide means of early diagnostics for endometrial cancer or monitoring for tumour recurrence following management. In the future, validation of these techniques is needed to prove their true value and improve the current approach to women with suspected endometrial cancer.

Current prognostics in endometrial cancer: Preoperative risk stratification models

Vít Weinberger[1], Vinklerová Petra[1], Ovesná Petra[1]
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The approach to endometrial cancer (EC) has dramatically changed over the last decade. We have shifted from a simple division into type 1 and 2 to molecular classification. Additionally, there are various serological and immunohistochemical (IHC) markers, which apparently affect a patient's prognosis. Acquiring as much preoperative information as possible plays a key role in decision-making. We need to adequately counsel the patient about surgery approach/extension and adjuvant treatment possibilities. With this presentation, I will depict several prognostic models that can be used for predicting individual patient outcome. Former models used traditional clinicopathological characteristics such as lymphovascular space invasion, myometrial invasion, histotype, grade, age, or BMI. However, it seems that results were insufficient and currently additional markers are readily used. Expression of hormonal receptors, L1CAM, p53, Ki67 are the most favorite IHC markers in predicting models. Some authors also include information from imaging methods: Tumor diameter, myometrial/cervical invasion, lymphadenopathy. The original means of multivariate analysis is based on a simple graphic calculating tool called nomogram. It is a two-dimensional diagram of regression coefficients designed to allow the estimation of probability. Using simple point connections in the graph provides individual clinical parameters within the total risk score which is associated with the probability of a monitored event. Decision tree learning is another type of predictive modeling approach used in statistics and machine learning computer algorithms. A decision tree works as a support tool using a tree-like model of decisions while indicating their potential consequences. With the development of computer technology, a Bayesian network has become more accessible. It is a probabilistic model that represents a set of variables and their conditional dependencies via a directed acyclic graph. It is used for determining probable relationships, causalities, and can be applied even when some patient characteristics are absent. Current prognostics models vary in types of outcome evaluation. Prediction of lymph node metastasis, overall survival, recurrence-free survival, disease-specific survival, or distinguishing between high and low-risk disease are most commonly employed. We present three examples to illustrate different types of prognostic models.

External validation study of endometrial cancer preoperative risk stratification (ENDORISK) model

Petra Vinklerová[1], Weinberger Vít[1], Ovesná Petra[2], Hausnerová Jitka[3], Pijnenborg MA Johanna[4], Lucas J. Peter[5], Reijnen Casper[4], Vrede W. Stephanie[4]

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IntroductionIn developed countries, endometrial cancer (EC) is a common malignancy with, generally, an excellent outcome. Nevertheless, despite a favorable prognosis, up to 15% of primary low-risk patients will experience recurrence and would profit from adjuvant treatment. Conversely, certain high-risk cases surprisingly evidence no disease after many years. With current emphasis on personalized medicine, we ideally seek as much information as possible concerning a patient's prognosis prior to effecting an appropriate treatment decision. ENDORISK is a machine-learning-based computational Bayesian networks model, which predicts with percentual probability LNM (lymph node metastasis) and 5-year DSS (disease-specific survival) in EC cases. The input data consists of preoperative clinical and histological characteristics. The model has been validated forthwith using two multicentric cohorts. Our objective was to confirm the ENDORISK model's effectiveness on our cohort with affirmed consistent adjuvant therapy and follow-up.

MethodsThe ENDORISK model was evaluated with a retrospective cohort of 425 patients from University Hospital Brno, Czech Republic. 299 patients were involved in our DSS analysis; 226 cases were available for LNM analysis. We also included patients with only a pelvic dissection or sentinel node biopsy, reflecting the current trend in EC diagnosis.

Results

The area under the curve (AUC) was 0.84 (95% CI, 0.77-0.9) for LNM (similar with validation cohort 0.82) and 0.87 (95% CI, 0.81-0.93) for 5-year DSS (validation cohorts 0.82 and 0.84). However, when using calibration plots to visualize the results, predictive value was outstanding for low-risk EC, although the results were overestimated among high-risk patients, especially in DSS.

Conclusion

Our data confirm the ENDORISK model's laudable predictive ability, particularly in patients with a low risk of LNM and favorable survival potential.

Section 3

Management of specific patients' subgroups

Fertility-sparing methods in adolescents affected by endometrial cancer

Krzysztof Gałczyński[1], Piotr Olcha[2,3], Aneta Adamiak-Godlewska[4], Aleksandra Kaminska[4], Sara Warysiuk[4], Katarzyna Romanek-Piva[2,4], Maciej Jóźwik[5], **Andrzej Semczuk[4]**

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Although in developed countries endometrial cancer (EC) is the most common gynecological malignancy, its occurrence in adolescents is exceedingly uncommon. The increasing rate of obesity in children and adolescents is held responsible for the increasing prevalence of EC in younger cohorts of patients. The diagnosis of this malignancy can have devastating consequences for future fertility because standard treatment protocols for EC include radical surgery. Here, we present the first detailed review of the world literature on EC in subjects aged 21 years or younger (n = 19). The mean age at diagnosis was 16.7 ± 0.6 years. One patient (5.3%) had a Type II (high-risk) disease. No communication retrieved from the search reported on patient death; however, two (10.5%) patients were lost to follow-up. There was also a high proportion (five subjects, 26.3%) of cases with genetic background (Cowden syndrome and Turner syndrome), therefore genetic screening or a direct genetic study should be considered in very young patients with EC. Such information, obtained from studies on older women, translates well to adolescent girls and very young women. Careful anatomopathological monitoring at follow-up is essential for the safety of a conservative approach. Improved survival in very young EC patients makes the preservation of fertility a central survivorship issue, therefore both patients and caregivers should undergo counseling regarding available options. Moreover, our study suggests that genetic syndromes other than Lynch syndrome may be associated with EC more frequently than previously thought.

How to manage elderly patients with endometrial cancer

Vita Andreja Mesarič[1], Nataša Kenda Šuster[2], Luka Roškar[1], Boštjan Pirš[1,2], Špela Smrkolj[1,2]
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Endometrial cancer is the most common gynaecological cancer in the developed countries and predominantly affects elderly women. Due to ever-aging population the number of patients with endometrial cancer is going to continue to rise and the patients are going to be older and older at the time of the diagnosis. Studies have shown that the overall survival of the elderly women with endometrial cancer is worse than that of their younger counterparts. This can be attributed to more aggressive types of endometrial cancer, that are more common in older patients, later stage at the diagnosis and the fact that the elderly patients are more often undertreated. It is well-known that obesity and diabetes are risk factors for the development of the endometrial cancer. At the same time, they represent comorbidities that influence the type of the rate of surgical and anesthesiological complications. We have to be aware of all the risk factors present and think about alternative treatment options, such as levonorgestrel IUD, radiotherapy only and/or vaginal hysterectomy. According to the guidelines the treatment for elderly and frail patients should be planned carefully by a multidisciplinary team that should perform a geriatric assessment of the patients and decide on the most appropriate treatment strategy. Comprehensive geriatric assessment (CGA), encompasses the somatic, functional and psychosocial domains of the patient and provides an objective evaluation of the health status and frailty of the patient. Studies have shown that treatment options that are in agreement with the CGA have a favourable impact on patient's health, functional status, the rate of complications and death rate. The treatment decision should balance the risk factors and the health status of these older patients using a multidisciplinary approach and should not be done based only on patients' age but rather focus on the frailty status and physiological, psychological and social circumstances.

How to manage patients at hereditary risk of endometrial cancer

Fabio Barra[1]
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Hereditary endometrial cancer makes up approximately 2% to 5% of all cases of endometrial cancer. Lynch syndrome and Cowden syndrome are the two most common inherited syndromes known to increase a woman's lifetime risk of endometrial cancer. In particular, it has been estimated that endometrial cancer is the sentinel malignancy in approximately 40% to 60% of patients with Lynch syndrome. Identification of women at higher risk of endometrial cancer may allow for the early detection of cancer and strategic measures to reduce development of subsequent cancer through risk reducing surgery. Women impacted by these inherited susceptibility syndromes benefit from reproductive counseling with implications for offspring and extended family. Patients may warrant further evaluation through genetic counseling and/or referral to an oncologic specialist if they were diagnosed with endometrial cancer at a young age (<50 years old), have a strong family history of malignancies, or a personal history of bilateral or multiple cancers. At our institution (IRCCS Ospedale Policlinico San Martino, Genoa, Italy) there is a regional reference center for managing women at high risk of developing a hereditary gynecological cancer (coordinator: dott. Maria Grazia Centurioni). The aim of this short talk is to give an overview on screening, diagnosis, and management of endometrial of endometrial cancer in patients at higher risk for endometrial cancer.

Short oral presentations

Molecular characterization of endometrial cancer: a single-institution preliminary experience

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Introduction
Since the Cancer Genome Atlas (TCGA) identified four molecular groups (POLEmut/MMRd/NSMP/TP53mut) of endometrial carcinoma many efforts have been spent to introduce molecular classification in diagnostic practice. This is also strongly recommended by ESGO/ESTRO/ESP 2020 guidelines. We evaluated the applicability of a custom NGS gene panel to define the right molecular subgroup and the relative risk class.
Methods
Our preliminary analysis included low-grade endometrioid (LGEC), high-grade endometrioid (HGEC) and serous carcinomas (SEC). Each case has been investigated with a panel of immunohistochemistry (IHC) including ERα, PR, Ki67, p53, β-catenin, e-cadherin, bcl-2, cyclin D1 and MMR proteins. After a standardized pre-analytical phase, the tumor DNA was semi-automatically extracted and analyzed with Oncomine On Demand Tumor Specific custom panel on 14 genes (BRIP, CTNNB1, KRAS, MLH1, MLH3, MSH2, MSH6, PALB2, PMS2, POLE, PTEN, TP53, RAD51C e RAD51D).
Results
32 cases were considered (n=16 LGEC, n=8 HGEC, n=8 SEC). The three histotypes showed significant morpho-molecular differences. The NGS analysis gave good analytical results except in one case. According to the new diagnostic algorithm we identified: POLEmut (n= 2), MMRd (n= 7), NSMP (n= 13), TP53mut (n= 9). The molecular-based risk assessment showed a partial overlap with the morphological-based one except in two cases (one downgraded and one upgraded after the application of molecular classification).
Conclusions
The preliminary results showed that our pre-analytical and analytical protocols are in keeping with the standards requested for molecular classification and therefore providing a more accurate risk-assessment of patients affected by endometrial cancer.

Inter-component immunohistochemical assessment of selected proliferative markers in uterine carcinosarcomas

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Objective

The aim of this retrospective study was to compare the immunohistochemical proliferation markers (Ki67, PCNA, MCM3 and topoisomerase IIα) assessment in both components of uterine carcinosarcoma (UC).

Materials and Methods

Thirty paraffin-embedded slides of UCs, obtained from patients who underwent surgery between 2006–2020 were analyzed. Medical records and clinicopathological patients' data were reviewed. Formalin-fixed, paraffin-embedded tissue sections were immunostained with monoclonal antibodies against Ki67, PCNA, MCM3 and topoisomerase IIα.

Results

Ki67-positive nuclear immunoreactivity was reported in 20 (67%) and 16 (53%) UC carcinomatous and sarcomatous components, respectively. In the epithelial component, Ki67 positive staining was related to FIGO stage (p=0.025), and histological grade (G1 vs G2/G3, p=0.031). Nuclear PCNA reactivity was noted in 18 (60%) and 16 (53%) carcinomatous and sarcomatous components, respectively. Interestingly, all four cases with omental metastases were PCNA-positive, and a relationship between staining pattern and the existence of metastases was of significant value (p=0.018). MCM3-positive nuclear staining was found nearly twice as high in the carcinomatous (n=19,63%), than in the sarcomatous (n=11, 37%) component, respectively, and MCM3 expression in the epithelial component was related to clinical stage (p=0.030), and the existence of omental metastasis (p=0.012). In addition, out of the thirty UCs, 17 (57%) and 13 (43%) showed topoIIα positivity in the carcinomatous and sarcomatous UC components, respectively. A significant relationship between protein immunoreactivity with FIGO stage (p=0.049), and omental metastasis (p=0.026) was found to exist. However, no significant differences between proliferation markers expression and clinico-pathological features in the sarcomatous UC component were indicated. Finally, a significant correlation between each protein IHC staining was demonstrated, particularly in the sarcomatous UC component.

Conclusion

A combined analysis of Ki67, PCNA, MCM3, and topoIIα may provide more detailed information of cell-cycle alterations determining the heterogeneity of uterine carcinosarcomas.

Serous endometrial carcinoma and pathogenic variants in genes of homologous recombination

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Endometrial carcinoma is the most frequent gynaecological malignancy in the Western world, with around 100.000 cases in Europe each year. Endometrial carcinoma is traditionally divided into two histopathological groups, type I endometrioid adenocarcinomas and type II group of non-endometrioid carcinomas. Latest, molecular classification divides endometrial carcinomas into 4 distinct subgroups with specific molecular characteristics. The fourth subgroup, with a high level of somatic copy-number alterations and with somatic TP53 mutations, is a group of carcinomas with an aggressive growth pattern, with early metastasis and poor outcome. The most common representative is serous endometrial carcinoma. The group also includes clear cell carcinoma, uterine carcinosarcoma, and high-grade endometrioid carcinoma. The main characteristic of serous endometrial carcinoma is a high level of somatic pathogenic variant TP53 and histological features, which are associated with high-grade ovarian carcinoma. Studies have demonstrated a possible link between serous carcinoma and BRCA1/-2 mutation or a mutation in other homologous recombination genes (e.g., ATM, BARD1, BRIP1, CHEK2, NBN, RAD51C). Determining specific »genomic scars«, which are caused by failed repair of double-stranded breaks in DNA with functional assays, is a way to determine changes in homologous recombination genes. Examples of such alterations that are overrepresented in BRCA1/2-null tumors include COSMIC Signature 3 and somatic copy-number alterations profiles associated with widespread loss of heterozygosity, large-scale state transitions, and telomeric allelic imbalances .Clear evidence of the link would confirm the importance of testing for homologous recombination deficiency in women with a diagnosis of serous endometrial carcinoma regardless of family history and could open a path to new ways of treatment.

Immunotherapy in endometrial carcinoma

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In the last 10 years, clinical oncology has been revolutionized by the introduction of oncological immunotherapy, mainly in the form of immune checkpoint inhibitors (ICIs) that transformed the standard of care of several advanced solid malignancies. Using ICIs for advanced gynaecological cancers has yielded good results, especially for endometrial cancer (EC). Until recently, therapies for patients with recurrent or metastatic EC in second line usually consisted of platinum-based chemotherapy and hormonal therapy yielding median progression free survival (mPFS) of less than 12 months. Being the solid tumour with highest incidence of mismatch repair deficiency and relatively high proportion of high tumour mutational burden (known biomarkers of ICI efficacy) there is certainly rationale for immunotherapy in endometrial cancer. Indeed, studies of ICIs in MMR deficient EC have shown good results – objective response rates (ORR) of up to 57% and mPFS up to 26 months. In MMR proficient EC, results were worse. However, with addition of antiangiogenic agents ORRs up to 31% and doubling of mPFS (compared with chemotherapy) were observed. We can expect increased use of ICIs combined with other agents and use of immunotherapeutic agents with novel mechanisms of action in endometrial cancer in the near future. This will create a need for reliable response prediction tools, which we believe will be based on biomarker, clinical, and tumour characteristics.

PTmomics for biomarker discovery and personalized treatment

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Posttranslational modifications (PTMs) are a set of modifications that occur once a protein leaves the ribosomal biosynthetic pathway. Malfunctions in the machinery creating those modifications can lead to diseases such as cancer. Thus, the PTM profile of a tumor can provide important information about potential biomarkers which can be of great importance for further research. At Sciomics we have established a high-throughput antibody microarray platform to identify differences in protein levels of a wide variety of different target proteins while requiring smallest sample amounts. In addition to determining the protein abundance in a large variety of samples, we also provide additional information about the status of a specific post-translational modification. We currently aim to adapt the platform by integrating two PTM measurements with a simultaneous detection of protein abundance in a single experiment. In a first step we optimized the experimental conditions of our PTM assays in order to maximize sensitivity and specificity and to reduce cross reactivities of the anti-PTM antibodies to spotted antibodies on the microarray surface. Furthermore, two different PTMs were detected in two individual experiments and the data was combined using a newly developed bioinformatical routine. First proof-of-concept experiments were performed, and we were able to successfully detect two different PTMs in one microarray experiment. Simultaneous measurements of protein, phosphorylation, and acetylation would provide new insights into the fundamental biological processes of carcinogenesis, making it possible to conduct PTM analysis on antibody microarrays in a more efficient and precise manner. This information, as shown in previous studies analyzing protein and multiple PTMs in endometrial cancer, could greatly advance research in this area.

Section 5

Importance of biobanking and national clinical data repositories

What should clinicians and researchers know about biobanking

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Establishing high quality biobanking standards in the clinic requires large and unified biobanks to guarantee a sustainable biobank infrastructure. Since 10 years Hannover Medical School (MHH) operates the Hannover Unified Biobank (HUB) which organizes standardized sample preparation, storage, and distribution as well as harmonization of sample related data. The HUB is connected by a transport service to the MHH and provides a rapid sample exchange and sample preparation with all clinics, operating rooms, and research institutes. Samples are processed with a high level of automation. Robotics is used for blood fractionation and aliquotting and fully automated DNA extraction ensures high sample quality. 1D/2D codes for permanent sample tracking together with the direct connection of the scanners and robotics to the central LIMS database system guarantee a streamlined data flow. The long-term storage of the biomaterial is realized in liquid nitrogen tanks, which are located in a modern, secured infrastructure. Samples and racks are compiled by an automated -80°C BIOS system. Sample related data, including the complete sample tracking information is documented and securely stored in the LIMS. A quality management system ensures the compliance to standards. Additionally, the HUB is certified according to DIN ISO 9001. Access to samples and data of the biobank and the linked clinical data warehouse of the MHH is organized in standardized procedures. It requires the approval and prioritization of the requesting research projects and the approval of the sample owner. The biobank is also open for national and international collaborations, networks and scientists.

IKNL and the Netherlands Cancer Registry

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The Netherlands Comprehensive Cancer Organisation (IKNL) is a knowledge and quality institute which aims to reduce the impact of cancer. IKNL enables health care professionals, researchers, policy makers and others to reflect on cancer and palliative care with the help of data from the Netherlands Cancer Registry (NCR). IKNL translates these data into valuable insights to improve oncological and palliative care by 1) supporting epidemiological studies, 2) supporting and evaluating clinical studies and 3) by developing and evaluating guidelines. IKNL is funded by the Ministry of Health, Welfare and Sport and has more than 500 employees. It has regional offices all over the country in order to maintain relationships with the regional cancer network organisations. Central offices are situated in Utrecht and Eindhoven. In the NCR, data of all new cancers diagnosed are collected by for about 140 trained registration clerks who work in 'in' the hospitals. The NCR relies on pathological cancer notifications via the Nationwide Histopathology and Cytopathology Data Network and Archive (PALGA) and has a coverage of 95%. Vital status and date of death or emigration were obtained from the Personal Records Database (BRP). The NCR contains three kinds of data sets: an A set) with information about the patient (date of birth, vital status) and diagnosis (date, histological subtype, grade), a B set) with more extensive data about the cancer (stage of disease (TNM), treatment, details of treatment). Next to this, IKNL collects data on the request of researchers which are not regularly collected in the NCR, for example for clinical audits or funded research projects. These data are collected in the C set. Data of the NCR are used by researchers and care professionals. IKNL handles more than >300 data requests yearly. IKNL researchers are often involved in interpretation of the data and as a result about 300 scientific publications with data from the NCR are published each year.

Slovenian Population-Based Cancer Registry – A database for monitoring national cancer burden and cancer care

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The Slovenian Cancer Registry (SCR) is recognized as one of the oldest and best quality population-based cancer registries in Europe and the world. Founded in 1950, from the very beginning it has operated under the auspices of the Institute of Oncology Ljubljana. In Slovenia, cancer reporting has been mandatory and prescribed by law since the foundation of the SCR. All healthcare institutions in Slovenia and other entities delivering healthcare activities must regularly report new cases of cancer to the SCR. Data on new cancer cases (incidence), survival and prevalence amassed in the SCR, together with mortality data collected and processed by the National Institute of Public Health, form the basis for assessing cancer burden in the country. The Registry's data are important for planning and evaluation of the National Cancer Control Programme for the primary and secondary prevention of cancer, diagnostics, treatment and rehabilitation, as well as for planning for the facilities and resources needed for cancer management (staff, medical equipment, hospital facilities). They are also extremely useful for Slovenian and international clinical and epidemiological research and for evaluating the effectiveness of screening programmes. In addition, precise data on diagnosis and treatment that the SCR manages in clinical registries can be used to monitor the quality of care received by oncology patients. In the last years, in cooperation with experts from the clinical environment, several national clinical cancer registries have been developed and established. As the first, the national Clinical Registry of Cutaneous Melanoma was launched, Registry of Lung Cancer was established in 2020, which is followed by national clinical registries for breast, prostate, colorectal and childhood cancers.

Slovenian biobank: Where we are and where we are going?

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Slovenian Biobanking and Biomolecular Resources Research Infrastructure Consortium BBMRI.SI was established in December 2020. Its founding members are all three Slovenian public universities - University of Maribor, University of Ljubljana, and University of Primorska - as well as University Medical Center Maribor. University of Maribor acts as the coordinating institution and its Vice-Rector for Knowledge Transfer Prof. Dr. Urban Bren as the national node coordinator. In 2021 we successfully became full members of the Biobanking and Biomolecular Resources - European Research Infrastructure Consortium BBMRI-ERIC. What lies ahead is the challenging consolidation of the fragmented Slovenian biobanking landscape.

Section 6

Omics for biomarker discovery and personalized treatment I

Affinity-proteomics pipeline for a robust protein biomarker discovery and verification

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Protein profiling plays an essential part in today's biomedical research, striving to improve patients' quality of life by using molecular signatures for more precise diagnostic means and treatment guidance. At Sciomics, we have established an affinity-proteomics platform for robust protein biomarker discovery and verification. Using our advanced, fully immuno-based scioDiscover assay covering 1,438 proteins with high sensitivity novel biomarker candidates can be identified from minimal sample amounts, only a few microliters of plasma or serum. Having the ability to analyse tissue, cells as well as body fluid derived samples with the same assay enables the discovery of innovative biomarker candidates as well as to gain deep insights into the disease biology at the same time while eliminating the need for different assays for individual sample types and therefore increasing the robustness. Here, we present the platform, its application in protein biomarker development and examples from our biomarker development pipeline covering projects in oncology, organ failure as well as COVID-19 aiming at enabling Precision Medicine by innovative protein biomarker signatures.

BioEndoCar: Identification of protein biomarker candidates for endometrial cancer using the ScioDiscover platform

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Today, non-invasive methods for diagnosis and stratification of endometrial cancer patients are lacking. Therefore, clinicians rely on histopathology and surgical findings as a gold standard. The BioEndoCar clinical study addresses the lack of easily accessible and reliable diagnostic and prognostic biomarkers. Blood samples from seven clinical centers around Europe were collected according to strict standard operating procedures and clinically annotated. In order to identify protein biomarker candidates, we aimed to compare endometrial cancer and control plasma samples. The scioDiscover antibody array platform is a fully immune-based technology with a broad coverage of biomedically relevant proteins, which allows highly multiplex protein profiling. Prior analysis, the samples were matched for age distribution and body-mass-index and randomized. A total of 302 samples, including 167 endometrial cancer samples and 135 control samples were profiled for more than 900 proteins. In this study, the scioDiscover assay showed an excellent technical performance with low technical variation. In addition to the routine technical quality control, the influence of the clinic of origin on the protein profile was investigated within the multi-centered trial. Here we describe the identification of a number of proteins with differential abundance in plasma samples from endometrial cancer and control samples. These markers represent promising candidates, which need to be confirmed. Ultimately, the generated data will be combined to metabolomic data in order to derive diagnostic and prognostic algorithms with even greater potential.

Experience the next generation multiplexing with Luminex® xMAP® INTELLIFLEX system

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Multiplex assays are a type of immunoassay capable of simultaneous measurement of multiple analytes. Luminex® xMAP® technology combines advanced fluidics, optics and digital signal processing with proprietary microsphere technology to deliver both high-density and high-throughput multiplexed assay capabilities at the same time. We will introduce xMAP® INTELLIFLEX system, the latest addition to the Luminex® portfolio of instruments. It is a flow-based, multiplex platform that simplifies workflows by combining the established performance of xMAP® technology with advanced features to elevate assay performance and empower innovation in assay development. By combining low and high-plex capabilities, the xMAP® INTELLIFLEX system gives fast, reliable results. We will also introduce MILLIPLEX® multiplex assays based on Luminex® xMAP® technology that offer applications throughout the life sciences and capabilities across a variety of bioassays. With over 1,000 analytes available for measurement of protein biomarkers and intracellular proteins, MILLIPLEX® assays represents the largest and fastest growing portfolio of multiplex biomarker assays.

Angiogenic factors as diagnostic and prognostic biomarker candidates for endometrial cancer

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In endometrial cancer (EC), preoperative determination of the disease extent would avoid the complications associated with radical surgery. Screening of patients' plasma biomarkers might enable a more precise diagnosis of EC and a tailored treatment approach. In the present study 37 angiogenic factors (AF) were investigated as potential biomarkers for EC. 76 postmenopausal women (38 patients with endometrioid EC and 38 control patients with benign gynecological condition) were included in this prospective case-control pilot study. AF concentrations were measured in preoperative plasma samples using Luminex xMAP™ multiplexing technology. Plasma levels of sTie-2 and G-CSF were significantly decreased in patients with EC compared to the control group, whereas the concentration of leptin was significantly higher in patients with EC. The neuropilin-1 level was significantly higher in patients with type 2 EC (gradus 3) in comparison to lower gradus patients or controls. Follistatin level was significantly higher in patients with present lymphovascular invasion and IL-8 plasma level was significantly higher in patients with metastasis. The plasma concentrations of indicated AFs could represent an important additional diagnostic tool for early detection and characterization of EC and could guide the decision on the extent of surgery. Further studies with a larger number of patients are currently ongoing.

Approaching a non-invasive diagnosis of endometrial cancer by the analysis of protein biomarkers in cervical samples

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Introduction

Diagnosis of endometrial cancer (EC) is performed on approximately 14M women in US and Europe every year who present with abnormal vaginal bleeding. However, only 5-10% will have EC. The diagnostic process always requires minimally invasive or invasive samplings of the endometrium for pathological examination to diagnose/rule out EC. Here, we aim to decipher protein biomarkers in the fluid of cervical cytologies, i.e. pap-smears, to achieve a non-invasive diagnosis of EC.

Methods

The discovery phase consisted of a data-dependent acquisition (DDA) of cervical fluids from 60 patients (20 EC, 20 non-EC, 20 non-EC with cervical pathology), followed by a targeted verification by LC-PRM in cervical fluids of 234 patients (128 EC; 113 non-EC). A logistic regression model assessed by 10-k-fold cross validation was used to assess the power of protein panels to diagnose EC and differentiate between EC histological subtypes and grades. Furthermore, the highest performing biomarker was validated in an ELISA assay using the verification cohort. Analysis was performed using MaxQuant, Skyline, SPSS and R software.

Results

The discovery study determined 2,888 proteins contained in cervical fluids. Statistical analysis identified 75 significant proteins between EC and non-EC, and 58 were verified. Among those, 16 had an AUC > 0.75. A 3-protein panel allowed EC diagnosis with an AUC of 0.957 (93% sensitivity and 90% specificity). Additionally, a 5-protein panel was able to distinguish histological subtypes and grades with AUC values of 0.88 and 0.97, respectively. The best performing diagnostic protein was transferred to ELISA reaching an AUC of 0.927.

Conclusions

Proteomics applied to cervical fluids permitted to identify protein panels that permit a highly accurate non-invasive diagnosis of EC, in addition to the determination of histological subtypes and grades. Our results aim to impact the standard of care of EC diagnosis.

Section 7

Omics for biomarker discovery and personalized treatment II

Study design for omics revisited

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Integration of omics has been proven to explain complex human phenotypes, disease progression and their heritability. Through the analyses of impact of genome on metabolome we have learned new interlaced control pathways and further discovered unexpected plasticity of environmentally driven signal transduction pathways. These integrative studies have their own requirements for study design, sample randomisation and normalisation of data. Not all study design strategies performing well in genomics can be directly applied to metabolomics or other functional studies like transcriptomics and metabolomics. Examples of design-flawed approaches will be shown to illustrate the impact of study design on the outcome and statistical analyses of data. Quality control procedures might be implemented to prevent flawed design.

Targeted and nontargeted metabolomics approaches in BioEndoCar

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Metabolomics aims to measure all metabolites in a given biological sample. Metabolites are small molecules with molecular masses below 1200 Da such as sugars, amino acids, acylcarnitines, organic acids, and lipids. Since metabolites are intermediates and final downstream products of all cellular processes, metabolomics is closest to the phenotype compared to the other 'omics'-techniques. With the advent of advanced analytical methods, which have a high level of sensitivity and wide metabolite coverage, metabolomics is increasingly applied in human health and biomedical research. In metabolomics, two approaches with different objectives are used, namely nontargeted and targeted metabolomics. Nontargeted metabolomics is a hypothesis-free approach aiming to detect simultaneously as many metabolites as possible. Therefore, nontargeted metabolomics is a versatile tool to search for biomarkers. Targeted metabolomics aims to determine the absolute concentrations of a pre-defined set of metabolites. Thus, targeted metabolomics is a hypothesis-driven approach and is very useful for validation of previously identified biomarkers. The Helmholtz Center Munich operates a state-of-the art core facility for mass spectrometry-based metabolomics and offers diverse assays in targeted and nontargeted metabolomics to collaboration partners and consortia. In BioEndoCar, we used a combination of nontargeted metabolomics with a wide-ranged targeted metabolomics approach. We were able to identify 640 metabolites with nontargeted metabolomics and determined the absolute concentration of 479 metabolites using a targeted metabolomics approach in patient and control plasma samples.

Machine Learning for OMICS data analysis in BioEndoCar

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BioEndoCar consortium partners have collected several hundreds of samples from human subjects with the goal to build robust prognostic and diagnostic models for endometrium carcinoma. Both metabolite and protein concentrations have been estimated from the collected samples. Combining this information with subjects' clinical background resulted in a large multi-omics dataset. A thorough data analysis is required in order to identify reliable biomarkers from such multi-omics datasets. While classical statistical analysis methods help to assess the contribution of each protein and metabolite feature separately, more sophisticated machine learning approaches help to analyse not only individual proteins or metabolites but also their non-linear interactions. To this end In BioEndoCar we have utilised a well-known machine learning model - the Random Forest. This model was trained on all possible subsets of BioEndoCar data: protein data, metabolomics data, and their combination with clinical data. Depending on the type of target variable (either diagnosis or prognosis) we have received two types of models: diagnostic and prognostic. We have then evaluated performance of both types separately.

Overall, we have seen great differentiating performance for the diagnostic models trained on metabolites (0.834 AUC), proteins (0.76 AUC), and their combination (0.801 AUC). However, prognostic models were unable to differentiate between low and high-risk patients with performance significantly different from that of a random classifier. These findings has been in line with the results of the classical statistical analysis, which has identified a few hundred significantly different proteins and metabolites between patients and controls while resulting in no significant metabolites and proteins between low and high-risk patients.

One of the dangers of applying powerful machine learning methods is overfitting. In other words, machine learning models are capable of using seemingly useful patterns from the training data, that however will not help to explain the unseen data. The risk of overfitting is especially high when working with very high dimensional data, such as dataset collected in BioEndoCar. To mitigate the risk of overfitting in our analysis, we have used a 20 times repeated 4 fold cross-validation algorithm that produces an average estimate of the model over four folds, making the assessment of the model's performance a lot more robust and informative. Moreover, we have chosen the area under the receiver operating characteristic curve as an ultimate performance measure to avoid the effects of slightly imbalance classes on our results.

Identification of protein biomarkers in FFPE primary tissues to predict recurrence in endometrial cancer

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Introduction

Endometrial cancer (EC) is the fourth most common cancer in women in developed countries and the sixth cause of death due to cancer. The clinicopathological classification, considered to be the gold standard, is inaccurate to predict tumor recurrence, which is the most important cause of death in EC patients. We aim to identify and verify predictive biomarkers of recurrence for different subtypes of EC, specifically, for endometrioid EC (EEC) at intermediate-to-high risk of recurrence, and for serous EC (SEC), which are at high risk of recurrence.

Methods

This study was approved by the Ethical Committee of each institution. FFPE primary tissues from a cohort of 102 patients including 64 intermediate-to-high risk EEC and 38 SEC were selected from Vall d'Hebron Hospital (Barcelona) and Arnau de Vilanova Hospital (Lleida). A discovery study comparing recurrent vs non-recurrent patients was performed using an untargeted label-free proteomic approach in the LTQ-Orbitrap Fusion Lumos. Verification of significant proteins was performed in FFPE primary tissues from an independent cohort of 129 EEC patients using a targeted approach (LC-MS PRM). Statistical analysis was performed using R script and p-values lower than 0.05 were considered statistically significant.

Results

A total of 4,569 and 5,747 proteins were detected in EEC and SEC patients. We identified 439 and 56 proteins differentially expressed in recurrent vs non-recurrent EEC and SEC patients, respectively. From those, 169 peptides from 58 proteins were studied in primary tissues of 126 EEC patients. Five proteins were verified with a p-value lower than 0.05.

Conclusions

We unveiled the proteomic landscape of recurrent EC and identified 5 protein biomarkers that could be potentially used as predictive biomarkers of recurrence for intermediate-to-high risk EEC. These results are aimed to improve the standard of care of EC.

Section 8

Experimental models of endometrial cancer

***In vitro* modeling in endometrial cancer**

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The behaviour of endometrial cancer and consequently its impact on disease aggressiveness and spread is connected to molecular characteristics of the carcinoma. In recent years, cell lines are being used as in vitro tumour models. Through growing understanding of the biological landscape of endometrial cancer further focus when planning research using in vitro models needs to be given to the biological characteristics of specific cell lines. Historical characterization of endometrial cancer classifies it into Type I and Type II carcinomas. Type I are endometrioid carcinomas and Type II encompass non-endometrioid histological subtypes. Previous research has characterized common commercially available cell lines regarding their hormone status (oestrogen receptor – ER and progesterone receptor – PR) as well as p53 status for Type I endometrial carcinoma cell lines (AN3, ECC-1, EN, EN-1, EN-11, HEC-1A, HEC1B, Ishikawa, KLE, MFE-280, MFE-296, MFE-319) and Type II cell lines (ARK1, ARK2, HEC-155/180, SPEC-2). Individual attempts have furthermore assessed common markers of enhanced mobility and potential for invasion such as epithelial mesenchymal transition (EMT) in different cell lines. This analysis showed, that the cell lines Ishikawa, HEC-1A and KLE have differential expression profiles of EMT after being exposed to common systemic therapy. In light of these findings further research needs to incorporate the currently important clinico-pathological characteristics of endometrial cancer as well as the molecular groupings when performing in vitro research. Accounting for endometrial cancer tumour heterogeneity can lead to more focused and individualised therapeutics and consequently patient individualised treatment.

Three-dimensional models to accelerate therapeutic discoveries *in vitro*

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Over the last two decades, three-dimensional (3D) culture systems have been studied as an in vitro model for drug screening due to their ability to reproduce the main characteristics presented in solid tumours such as: (1) cell–cell signalling; (2) cellular heterogeneity; (3) internal structure; (4) ECM deposition; (5) cell–cell and ECM cell and interactions; (6) gene expression profile; (7) growth kinetics and (8) drug resistance. 3D tumour models are particularly relevant for different types of cancer research as well as for endometrial cancer since these tumour cells grow and metastasize from multicellular spheroidal aggregates. Scientists are increasingly using different tools for developing 3D models, including hydrogels, scaffold-based and scaffold-free, cancer-on-a-chip devices and bioprinting. The most commonly used 3D models of cancer for drug testing are multicellular tumour spheroid models, multilayer cell cultures, organoids, and cells implanted on porous biomaterial. Three-dimensional (3D) bioprinting is a promising and innovative bio-fabrication strategy to precisely position biologics, including living cells and extracellular matrix (ECM) components, in the prescribed 3D hierarchal organization to create artificial multi-cellular tissues/organs. The four most commonly used techniques for 3D bioprinting are extrusion bioprinting, stereolithography, laser-assisted bioprinting and inkjet bioprinting. 3D bioprinted models offering a platform for in vitro high-throughput, accurate and rapid drug discovery and screening for novel, combinatorial, and repurposed drugs, that could be easily replicated to different cell lines and can be used for drug efficacy, drug pathway, toxicity testing and models for exploring a tumour migration and invasion.

Estrogens in endometrial cancer

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Endometrial cancer (EC) is associated with increased estrogen actions, but the exact role of estrogens in EC of different grades is not entirely understood. In our study, we analyzed the local estrogen formation in cell lines of different grades and different menopausal statuses, Ishikawa (pre-menopausal, G1), HEC-1-A (post-menopausal, G2), RL95-2 (post-menopausal, G2), KLE (post-menopausal, G3), and in paired samples of EC and adjacent control tissues. We performed gene and protein expression analyses and studies on steroid precursors' uptake and metabolism. All cell lines efficiently transformed estrone sulfate precursor (E1-S) to estradiol but did not transform dehydroepiandrosterone sulfate (DHEA-S) to estrogens which confirmed the pivotal role of the sulfatase pathway for estradiol (E2) formation. In post-menopausal HEC-1-A cells, the formation of estrogens from E1-S was higher than in pre-menopausal Ishikawa cells due to low levels of ABCG2 and higher levels of several uptake transporters SLCO, as confirmed by gene expression analysis, immunocytochemistry, and gene silencing studies. In poorly differentiated KLE compared to moderately differentiated RL95-2 cells, we observed increased E1-S uptake associated with SLCO transporters, especially SLCO1A2, SLCO1B3, and SLCO1C1, as confirmed by expression analysis and inhibition studies. In these cells disturbed balance in expression of HSD17B genes led to enhanced activation of E1 to E2. In EC tissues compared to paired adjacent control tissue, we observed lower levels of efflux transporters ABCG2 and SLC51B. The expression of SLC51B was lower in patients with high-grade EC compared to patients with low-grade tumors. ECs of different grades differ in E1-S uptake and metabolism, which can be explained by differential levels of E1-S transporters ABCG2, SLC51B, and SLCO.

Androgens in endometrial cancer

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Endometrial cancer (EC) is generally a postmenopausal pathology with increasing incidence rate in a growing and aging population. Epidemiological studies have correlated androgens with an increased risk of EC. The role of these steroid hormones and especially that of their 11-oxygenated metabolites, i.e., 11-oxyandrogens in EC pathogenesis is still largely unknown. Objective: To explore the local androgen metabolism in EC using model cell lines. Methods: Gene expression of key enzymes involved in androgen metabolism was examined in cell lines of low- and high-grade EC. Further, cells were incubated with physiological levels of androgens (dehydroepiandrosterone sulfate (DHEA-S), DHEA, androstenedione (A4)), and 11-oxyandrogens (11b-hydroxy-A4, 11-keto-A4). The profile of androgen metabolites formed from each steroid precursor was assessed by LC-MS/MS. Results: Our gene expression data indicate that EC cell lines can potentially synthesize active androgens, i.e., testosterone (T) and 5α-dihydrotestosterone (5α-DHT) from androgen precursors, and equally potent 11-oxy-metabolites, 11-keto-T and 11-keto-DHT from adrenal 11-oxyandrogens. Indeed, incubation with DHEA-S, DHEA and A4 resulted with the formation of T and DHT, but not of 11-oxyandrogens. Interestingly, grade II and III EC cell lines synthesized higher T and DHT levels comparing to control and grade I cell lines. Moreover, EC lines metabolized 11-oxyandrogens to active 11-oxyandrogens. Curiously, low-grade EC lines synthesized greater 11-keto-T levels comparing to high-grade and control EC line. Conclusions: EC cell lines metabolize androgens to biologically active androgens. Moreover, EC lines metabolize 11-oxyandrogens to active 11-keto-T. The effect of androgen signaling on key cellular processes in EC is currently under investigation.This work was supported by the Slovenian Research Agency. Grant number: J3-2535.

Modelling endometrial cancer *in vivo*

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A major hurdle in translational endometrial cancer (EC) research is the lack of robust preclinical models that accurately capture endometrial cancer subtypes. Some endometrioid EC cell lines are available from commercial sources, however many of these show high mutation rates and large chromosomal rearrangements, not representative for most endometrioid cancers. For non-endometrioid types, very few cell lines are available. This has hampered the development of new treatment strategies for EC and limits the possibilities to perform relevant mechanistic studies. To overcome this problem, our lab has established EC organoids from resected patient tumor tissue and performed detailed genetic and transcriptomic characterization of these models. These models show great potential both for drug testing in vitro and in vivo, and are important tools to better understand context-dependencies in endometrial cancer.

Keynote lecture

Future directions in endometrial cancer management

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Endometrial cancer (EC) is the sixth most common malignancy in women with rising incidence due to advanced life-expectancy and obesity. The global EC-related mortality is estimated around 76,000 per year. Historically, EC is classified into Type 1 and Type 2 tumors, based on the observation of 'estrogen related' low-grade endometrioid histology and good prognosis in Type 1, and lack of 'estrogen related' Type 2 that is characterized by high grade histology with substantial worse outcome. In 2013 molecular profiling has identified four subgroups: POLE ultramutated tumors with excellent prognosis; hypermutated tumors with mismatch repair deficiency (MMRd); and tumors with no specific molecular profile (NSMP/p53wt) with intermediate prognosis, and copy number high with TP53 mutations (CNH/p53abn) with poor prognosis. Although molecular subgroups are present across all histological subgroups, Type 1 tumors are mainly represented by the NSMP group (90% low-grade; 85% FIGO I) and Type 2 by the CNH group (91% high-grade; FIGO I 45%). There is an ongoing debate whether lymph node status should be determined in all patients resulting in a wide variation in clinical practice. In the presence of lymph node metastasis (LNM), adjuvant therapy results in a 5-year survival rate of 65% compared to 5-10% when patients present with LNM in a recurrent setting. Sentinel node mapping has facilitated the evaluation of lymph node status with reduced surgical-related morbidity. As most EC patients (85%) have no LNM improved preoperative risk stratification can contribute to a selective surgical approach. Based on the presence of clinicopathological risk factors (tumor grade, lymphvascular space invasion, deep myometrial invasion) adjuvant radiotherapy can be applied for local control. Whereas chemotherapy has shown to improve survival in advanced stage. Molecular profiling is expected to further refine adjuvant therapy regimen and support the use of more targeted treatment options such as: immunotherapy, PARP inhibition, hormonal therapy. Patients with EC are often fragile, obese with multiple comorbidities, underlining the need for personalized approach both in primary and adjuvant therapy. The challenge in future treatment is balancing the benefits of new stratification tools, i.e. molecular, imaging, biomarkers, with patients' preferences and outcome to deliver the optimal individualized treatment approach.

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